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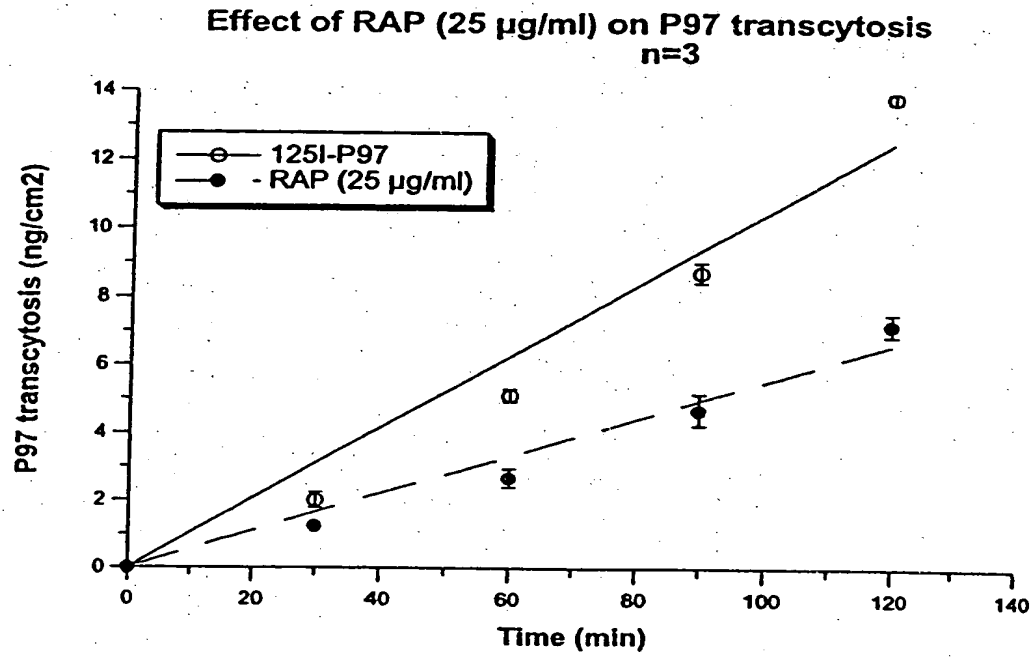


FIGURE 1

**FIGURE 2 Primers used to obtain sequences high-fidelity PCR amplification of human cDNA.**

RAPF: GCGATAGGATCCTACTCGCGGGAGAAGAACCAGCCCAAGCCGTCCCCGA (SEQ ID NO: 12)

RAPR: GCGATAAACCGGTTTCTGCCTCGGCGCGAGCTCTGGAGATCCTGCCGGACAGGTCCT (SEQ ID NO: 13)

GAAF: GCGATAACCGGTGCACACCCCGGCCGTCCAGAGCAGTG (SEQ ID NO: 14)

GAAR: GCGATACTCGAGTCAACACCAGCTGACGAGAACTGC (SEQ ID NO: 15)

IDUF: GCGATAACCGGTGAGGCCCCCGCACCTGGTGCATGTGGACGCGGC (SEQ ID NO: 16)

IDUR: GCGATACTCGAGTCATGGATTGCCCGGGGATGGGGGCCCTCTTGG (SEQ ID NO: 17)

GNDF: ACAGTGACCGGTTCAACCAGATAAACAATGGCA (SEQ ID NO: 18)

GDNR: ACAGTGCTCGAGTCTAGATCAGATACATCCACACCTTT (SEQ ID NO: 19)

**GNDF fusion, substitution of RAPF with RAPBACF in RAP amplification of GDNF construct.**

RAPBACF: ACAGTGGCCATGGGGGGTTCTTACTCGCGGGAGAAGAACCAGCCCAAGCCG (SEQ ID NO: 20)

**Figure 3. Nucleotide (SEQ ID NO:6) and protein (SEQ ID NO:7) sequences of the RAP-GAA fusion**

cttaccgccatgcggggtccgagcggggctctgtggctgctcctggctctgcgaccgtg  
M R G P S G A L W L L L A L R T V  
ctcggatcctactcgcggggagaagaaccagcccaagccgtccccgaaacgagtcgga  
L G S Y S R E K N Q P K P S P K R E S G  
gaggagttccgcatggagaagttgaaccagctgtgggagaaggcccagcgactgcattt  
E E F R M E K L N Q L W E K A Q R L H L  
cctcccggtgaggctggccgagctccacgctgatctgaagatacaggagagggacgaactc  
P P V R L A E L H A D L K I Q E R D E L  
gcctggaagaaactaaagccttgacggcttgacgaagatggggagaaggaagcgagactc  
A W K K L K L D G L D E D G E K E A R L  
atacgcaacctcaatgtcatcttgcccaagtatggtctggacggaagaaggacgctcgg  
I R N L N V I L A K Y G L D G K K D A R  
caggtgaccagcaactccctcagtgggcaccaggaagacgggctggatgacccaggctg  
Q V T S N S L S G T Q E D G L D D P R L  
gaaaagctgtggcacaaggcgaagacctctgggaaattctccggcgaagaactggacaag  
E K L W H K A K T S G K F S G E E L D K  
ctctggcgaggagttcctgcatacaaaagagaaagttcacgagtacaacgtcctgctggag  
L W R E F L H H K E K V H E Y N V L L E  
accctgagcaggaccgaagaaatccacgagaacgtcattagcccctcggacctgagcgac  
T L S R T E E I H E N V I S P S D L S D  
atcaagggcagcgctcctgcacagcaggcacacggagctgaaggagaagctgcgacgac  
I K G S V L H S R H T E L K E K L R S I  
aaccagggcctggaccgctgcgagggtcagccaccagggtacagcactgaggctgag  
N Q G L D R L R R V S H Q G Y S T E A E  
ttcgaggagcccagggtgattgacctgtgggacctggcgagtcggccaacctcacggac  
F E E P R V I D L W D L A Q S A N L T D  
aaggagctggaggcggttccgggaggagctcaagcacttcgaagccaaaatcgagaagcac  
K E L E A F R E E L K H F E A K I E K H  
aaccactaccagaagcagctggagattgcgcacgagaagctgaggcacgcagagagcgtg  
N H Y Q K Q L E I A H E K L R H A E S V  
ggcgacggcgagcggtgtgagccgcagccgcgagaagcacgcctgctggagggggcgacc  
G D G E R V S R S R E K H A L L E G R T  
aaggagctgggctacacggtgaagaagcatctgcaggacctgtccggcaggatctccaga  
K E L G Y T V K K H L Q D L S G R I S R  
gctcgcgccgaggcagaaaaccggtgcacacccccggcgtcccagagcagtgccacacag  
A R A E A E T G A H P G R P R A V P T Q  
tgcgacgtccccccaacagccgcttcgattgcgcccctgacaaggccatcacccaggaa  
C D V P P N S R F D C A P D K A I T Q E  
cagtgcgagggcccgcggtgctgctacatccctgcaaagcaggggctgcagggagcccag  
Q C E A R G C C Y I P A K Q G L Q G A Q  
atggggcagccctgggtgcttctccaccagctacccagctacaagctggagaacctg  
M G Q P W C F F P P S Y P S Y K L E N L  
agctcctctgaaatgggctacacggccaccctgacctgaccacccccaccttcttcccc  
S S S E M G Y T A T L T R T T P T F F P  
aaggacatcctgacctgcggtggagctgatgatggagactgagaaccgcctccacttc  
K D I L T L R L D V M M E T E N R L H F  
acgatcaaagatccagctaacaggcgctacgaggtgcccttgagagaccccgcggtgtccac  
T I K D P A N R R Y E V P L E T P R V H  
agccgggcaccgtccccactctacagcggtgagttctccgaggagcccttcgggggtgatc  
S R A P S P L Y S V E F S E E P F G V I

**Figure 3A**

gtgcaccggcagctggacggcgcgctgctgctgaacacgacggtggcgcccctgttcttt  
V H R Q L D G R V L L N T T V A P L F F  
gcccagcagttccttcagctgtccacctgctgccctcgagctatcacaggcctcgcc  
A D Q F L Q L S T S L P S Q Y I T G L A  
gagcacctcagtcacctgatgctcagcaccagctggaccaggatcacctgtggaaccgg  
E H L S P L M L S T S W T R I T L W N R  
gaccttgcccccacgcccgggtgcgaacctctacgggtctcacctttctacctggcgctg  
D L A P T P G A N L Y G S H P F Y L A L  
gaggacggcgggtgcggcacacgggggtgttcctgctaaacagcaatgccatggatgtggtc  
E D G G S A H G V F L L N S N A M D V V  
ctgcagccgagccctgccccttagctggaggctcgacaggtgggatcctggatgtctacac  
L Q P S P A L S W R S T G G I L D V Y I  
ttcctggggcccagagcccaagagcgtgggtgcagcagctacctggacgttggtgggatacccg  
F L G P E P K S V V Q Q Y L D V V G Y P  
ttcatgccgccatactggggcctgggcttccacctgtgccgctggggctactcctccacc  
F M P P Y W G L G F H L C R W G Y S S T  
gctatcacccgccaggtgggtggagaacatgaccagggccacttccccctggacgtccaa  
A I T R Q V V E N M T R A H F P L D V Q  
tggaacgacctggactacatggactcccgaggaggacttcacgttcaacaaggatggcttc  
W N D L D Y M D S R R D F T F N K D G F  
cgggactccccgcatgggtgcaggagctgcaccagggcgccggcgctacatgatgatc  
R D F P A M V Q E L H Q G G R R Y M M I  
gtggatcctgccatcagcagctcggggcctgccgggagctacaggccctacgacgagggt  
V D P A I S S S G P A G S Y R P Y D E G  
ctgcggaggggggttttcatcaccaacgagaccggccagccgctgattgggaaggtatgg  
L R R G V F I T N E T G Q P L I G K V W  
ccccgggtccactgccttccccgacttcaccaacccacagccctggcctgggtgggaggac  
P G S T A F P D F T N P T A L A W W E D  
atgggtggctgagttccatgaccaggtgcccttcgacggcttggtgattgacatgaacgag  
M V D Q V P F D G L W I D M N E  
ccttccaacttcatcagaggctctgaggacggctgcccccaacaatgagctggagaaccca  
P S N F I R G S E D G C P N N E L E N P  
ccctacgtgcctgggggtgggtggggggaccctccaggcgccaccatctgtgcctccagc  
P Y V P G V V G G T L Q A A T I C A S S  
caccagtttctctccacacactacaacctgcacaacctctacggcctgaccgaagccatc  
H Q F L S T H Y N L H N L Y G L T E A I  
gcctccacagggcgctgggtgaaggctcgggggacacgcccatttgtgatctcccgcctcg  
A S H R A L V K A R G T R P F V I S R S  
acctttgctggccacggccgatacggccactggacgggggacgtgtggagctcctgg  
T F A G H G R Y A G H W T G D V W S S W  
gagcagctcgctcctccgtgccagaaatcctgcagtttaacctgctgggggtgcctctg  
E Q L A S S V P E I L Q F N L L G V P L  
gtcggggccgacgtctgcggcttctgggcaacacctcagaggagctgtgtgtgcgctgg  
V G A D V C G F L G N T S E E L C V R W  
accagctgggggccttctaccccttcatgcggaaccacaacagcctgctcagctctgcc  
T Q L G A F Y P F M R N H N S L L S L P  
caggagccgtacagcttcagcgagccggccagcaggccatgaggaaggccctcacctg  
Q E P Y S F S E P A Q Q A M R K A L T L  
cgctacgcactcctccccacctctacacactgttccaccaggccacgtcgcgggggag  
R Y A L L P H L Y T L F H Q A H V A G E  
accgtggccccggccctcttctggagttccccaaggactctagcacctggactgtggac  
T V A R P L F L E F P K D S S T W T V D  
caccagctcctgtggggggaggccctgctcatcacccagtgctccaggccgggaaggcc  
H Q L L W G E A L L I T P V L Q A G K A

Figure 3B

gaagtgactggctacttcccccttgggcacatggtacgacctgcagacggtgccaatagag  
E V T G Y F P L G T W Y D L Q T V P I E  
gcccttggcagcctccccccccacctgcagctccccgtgagccagccatccacagcgag  
A L G S L P P P P A A P R E P A I H S E  
gggcagtgggtgacgctgccggccccctggacaccatcaacgtccacctccgggctggg  
G Q W V T L P A P L D T I N V H L R A G  
tacatcatccccctgcagggccctggcctcacaaccacagagtcccgccagcagcccatg  
Y I I P L Q G P G L T T T E S R Q Q P M  
gccctggctgtggccctaaccaaggggtggagaggccccgaggggagctgttctgggacgat  
A L A V A L T K G G E A R G E L F W D D  
ggagagagcctggaagtgctggagcgaggggcctacacacaggtcatcttcctggccagg  
G E S L E V L E R G A Y T Q V I F L A R  
aataacacgatcgtgaatgagctggtacgtgtgaccagtgagggagctggcctgcagctg  
N N T I V N E L V R V T S E G A G L Q L  
cagaaggtgactgtcctgggcgtggccacggcgccccagcaggtcctctccaacgggtgtc  
Q K V T V L G V A T A P Q Q V L S N G V  
cctgtctccaacttcacctacagccccgacaccaaggtcctggacatctgtgtctcgctg  
P V S N F T Y S P D T K V L D I C V S L  
ttgatgggagagcagtttctcgtcagctggtgttgactcgag  
L M G E Q F L V S W C -

**Figure 3C**

Melanotransferrin signal sequence is italicized. Linker peptide is underlined.

**FIGURE 4. Nucleotide (SEQ ID NO:8) and protein (SEQ ID NO:9) sequences of the RAP-IDU fusion**

aagcttaccgccatgcgggggtccgagcggggctctgtggctgctcctggctctgcgcacc  
M R G P S G A L W L L L A L R T  
gtgctcggatcctactcgcgaggagaagaaccagcccaagccgtccccgaaacgcgagtc  
V L G S Y S R E K N Q P K P S P K R E S  
ggagaggaggttccgcatggagaagttgaaccagctgtgggagaaggcccagcgactgcat  
G E E F R M E K L N Q L W E K A Q R L H  
cttctcccgtagggctggccgagctccacgctgatctgaagatacaggagaggacgaa  
L P P V R L A E L H A D L K I Q E R D E  
ctcgctggaagaaactaaagcttgacggcttgacgaagatggggagaaggaagcgaga  
L A W K K L K L D G L D E D G E K E A R  
ctcatacgcaacctcaatgtcatcttgcccaagtatggtctggacggaaagaaggacgct  
L I R N L N V I L A K Y G L D G K K D A  
cggcaggtgaccagcaactccctcagtggcaccaggaagacgggctggatgaccccagg  
R Q V T S N S L S G T Q E D G L D D P R  
ctggaaaagctgtggcacaaggcgaagacctctgggaaattctccggcgaagaactggac  
L E K L W H K A K T S G K F S G E E L D  
aagctctggcgagggtcctgcatacacaagagaaaagttcacgagtagaacgtcctgtg  
K L W R E F L H H K E K V H E Y N V L L  
gagaccctgagcaggaccgaagaaatccacgagaacgtcattagcccctcgacactgagc  
E T L S R T E E I H E N V I S P S D L S  
gacatcaagggcagcgtcctgcacagcaggcacacggagctgaaggagaagctgcgcagc  
D I K G S V L H S R H T E L K E K L R S  
atcaaccagggcctggaccgcctgcgcagggtcagccaccagggctacagcactgaggct  
I N Q G L D R L R R V S H Q G Y S T E A  
gagttcgaggagccagggtgattgacctgtgggacctggcgagtcggccaacctcacg  
E F E E P R V I D L W D L A Q S A N L T  
gacaaggagctggaggcggttccgggaggagctcaagcacttcgaagccaaaatcgagaag  
D K E L E A F R E E L K H F E A K I E K  
cacaaccactaccagaagcagctggagattgcgacgagaagctgaggcacgcagagagc  
H N H Y Q K Q L E I A H E K L R H A E S  
gtgggagcagggcagcgtgtgagccgcagccgcgagaagcacgccctgctggaggggagg  
V G D G E R V S R S R E K H A L L E G R  
accaaggagctgggctacacggtgaagaagcatctgcaggacctgtccggcaggatctcc  
T K E L G Y T V K K H L Q D L S G R I S  
agagctcgcgccgaggcagaaaccggtgaggcccgacactgggtgcatgtggacgcggcc  
R A R A E A E T G E A P H L V H V D A A  
cgcgcgctgtggccccctgcggcgcttctggaggagcacaggcttctgcccccgctgcc  
R A L W P L R R F W R S T G F C P P L P  
cacagccaggctgaccagtacgtcctcagctgggaccagcagctcaacctcgcctatgtg  
H S Q A D Q Y V L S W D Q Q L N L A Y V  
ggcgccgtccctcaccgcggcatcaagcaggtccggacccactggctgctggagcttgctc  
G A V P H R G I K Q V R T H W L L E L V  
accaccagggggtccactggacggggcctgagctacaacttcacccacctggacgggtac  
T T R G S T G R G L S Y N F T H L D G Y  
ttggaccttctcaggggagaaccagctcctcccagggtttgagctgatgggcagcgctcg  
L D L L R E N Q L L P G F E L M G S A S  
ggccacttcactgactttgaggacaagcagcaggtgtttgagtgaaggacttggtctcc  
G H F T D F E D K Q Q V F E W K D L V S  
agcctggccaggagatacatcggtaggtacggactggcgcatgtttccaagtggaaacttc  
S L A R R Y I G R Y G L A H V S K W N F

**Figure 4A**

gagacgtggaatgagccagaccaccacgactttgacaacgtctccatgaccatgcaaggc  
E T W N E P D H H D F D N V S M T M Q G  
ttcctgaactactacgatgcctgctcggagggtctgcgcgccgcccagccccgccctgagg  
F L N Y Y D A C S E G L R A A S P A L R  
ctgggaggccccggcgactccttccacacccccaccgcatccccgctgagctggggcctc  
L G G P G D S F H T P P R S P L S W G L  
ctgcgccactgccacgacggtaccaacttcttactggggaggcgggcgctgcggctggac  
L R H C H D G T N F F T G E A G V R L D  
tacatctccctccacaggaagggtgcgcgcagctccatctccatcctggagcaggagaag  
Y I S L H R K G A R S S I S I L E Q E K  
gtcgtgcgcgcagcagatccggcagctcttcccccaagttcgcggacacccccatttacaac  
V V A Q Q I R Q L F P K F A D T P I Y N  
gacgaggcgaggccccgctgggtgggtgggtccctgccacagccgtggaggcgaggacgtgacc  
D E A D P L V G W S L P Q P W R A D V T  
tacgcggccatgggtgggtgaagggtcatcgcgcagcatcagaacctgctactggccaacacc  
Y A A M V V K V I A Q H Q N L L L A N T  
acctccgccttccccctacgcgctcctgagcaacgacaatgccttccctgagctaccacccg  
T S A F P Y A L L S N D N A F L S Y H P  
cacccttccgcgcagcgcacgctcaccgcgcgcttccagggtcaacaacacccgccccgcg  
H P F A Q R T L T A R F Q V N N T R P P  
cacgtgcagctgttgcgcaagccggtgtcgcggccatggggctgctggcgctgctggat  
H V Q L L R K P V L T A M G L L A L L D  
gaggagcagctctggggccgaagtgtcgcgaggccgggaccgtcctggacagcaaccacag  
E E Q L W A E V S Q A G T V L D S N H T  
gtggggcgtcctggccagcgcgccaccgccccagggcccgccgacgcctggcgcgccgcg  
V G V L A S A H R P Q G P A D A W R A A  
gtgctgatctacgcgcagcgcagacacccgcgcgccaccccaaccgcagcgtcgcggtgacc  
V L I Y A S D D T R A H P N R S V A V T  
ctgcggctgcgcgggggtgccccccggcccgggcctgggtctacgtcacgcgctacctggac  
L R L R G V P G P G L V Y V T R Y L D  
aacgggctctgcagccccgcaggcgagtgggcgccgctggggccggcccgcttccccacg  
N G L C S P D G E W R R L G R P V F P T  
gcagagcagttccggcgcatgcgcgcgggtgaggacccgggtggccgcggcgccccgcccc  
A E Q F R R M R A A E D P V A A A P R P  
ttacccgcggcgccgcctgaccctgcgcgccgcgctgcggctgccgtcgcttttgctg  
L P A G G R L T L R P A L R L P S L L L  
gtgcacgtgtgtgcgcgccccgagaagccgccccgggacaggtcacgcggctccgcgcctg  
V H V C A R P E K P P G Q V T R L R A L  
cccctgacccaagggcagctgggtctgtgtcggatgaacacgtggggtccaagtgc  
P L T Q G Q L V L V W S D E H V G S K C  
ctgtggacatacagatccagttctctcaggacggtaaggcgtacaccccggtcagcagg  
L W T Y E I Q F S Q D G K A Y T P V S R  
aagccatcgaccttcaacctctttgtgttcagcccagacacaggtgctgtctctggctcc  
K P S T F N L F V F S P D T G A V S G S  
taccgagttcgcagccctggactactgggcccgcaccagggcccttctcggacctgtgccg  
Y R V R A L D Y W A R P G P F S D P V P  
tacctggagggtccctgtgccaagaggcccccatccccgggcaatccatgactcgag  
Y L E V P V P R G P P S P G N P -

**Figure 4B**

Melanotransferrin signal sequence is italicized. Linker peptide is underlined.

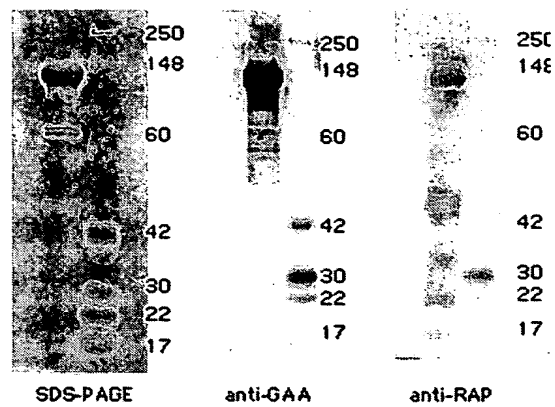


**FIGURE 5. Nucleotide (SEQ ID NO:10) and protein (SEQ ID NO:11) sequences of the RAP-GDNF fusion**

atgggggggttcttactcgcgaggagaagaaccagcccaagccgtccccgaaacgcgagtc  
 M G G S Y S R E K N Q P K P S P K R E S  
 ggagaggaggttccgcatggagaagttgaaccagctgtgggagaaggcccagcgactgcat  
 G E E F R M E K L N Q L W E K A Q R L H  
 ctctctcccgtagggctggccgagctccacgctgatctgaagatacaggagagggacgaa  
 L P P V R L A E L H A D L K I Q E R D E  
 ctgcctggaagaaactaaagcttgacggccttgacgaagatggggagaaggaagcgaga  
 L A W K K L K L D G L D E D G E K E A R  
 ctcatacgcaacctcaatgtcatcttgcccaagtatggtctggacggaaagaaggacgct  
 L I R N L N V I L A K Y G L D G K K D A  
 cggcaggtgaccagcaactccctcagtgccacccaggaagacgggctggatgaccccagg  
 R Q V T S N S L S G T Q E D G L D D P R  
 ctggaaaagctgtggcacaaggcgaagacctctgggaaattctccggcgaagaactggac  
 L E K L W H K A K T S G K F S G E E L D  
 aagctctggcgagggttcctgcacacagaaagttcacgagtacaacgtcctgctg  
 K L W R E F L H H K E K V H E Y N V L L  
 gagaccctgagcaggaccgaagaaatccacgagaacgtcattagccccctcgacactgagc  
 E T L S R T E E I H E N V I S P S D L S  
 gacatcaagggcagcgctcctgcacagcaggcacacggagctgaaggagaagctgcgacg  
 D I K G S V L H S R H T E L K E K L R S  
 atcaaccagggcctggaccgcctgcgcaggggtcagccaccagggtacagcactgaggt  
 I N Q G L D R L R R V S H Q G Y S T E A  
 gagttcgaggagcccgaggtgattgacctgtgggacctggcgagctccgccaacctcacg  
 E F E E P R V I D L W D L A Q S A N L T  
 gacaaggagctggaggcggttcgggaggagctcaagcacttcgaagccaaaatcgagaag  
 D K E L E A F R E E L K H F E A K I E K  
 cacaaccactaccagaagcagctggagattgcgcacgagaagctgaggcacgcagagagc  
 H N H Y Q K Q L E I A H E K L R H A E S  
 gtgggagcagggcgagcgtgtgagccgcagccgcgagaagcacgccctgctggaggggagg  
 V G D G E R V S R S R E K H A L L E G R  
 accaaggagctgggctacacgggtgaagaagcatctgcaggacctgtccggcaggatctcc  
 T K E L G Y T V K K H L Q D L S G R I S  
 agagctcgggcccaggcagaaaccgggttcaccagataaaacaaatggcagtgcttcctaga  
R A R A E A E T G S P D K Q M A V L P R  
 agagagcgggaatcggcaggctgcagctgccaaaccagagaattccagaggaaaaggctcgg  
 R E R N R Q A A A A N P E N S R G K G R  
 agaggccagagggggcaaaaaccggggttggtgtcttaactgcaatacatttaaattgtcact  
 R G Q R G K N R G C V L T A I H L N V T  
 gacttgggtctgggctatgaaaccaaggaggaactgatttttaggtactgcagcggtctct  
 D L G L G Y E T K E E L I F R Y C S G S  
 tgcgatgcagctgagacaacgtacgacaaaatattgaaaaacttatccagaaatagaagg  
 C D A A E T T Y D K I L K N L S R N R R  
 ctgggtgagtgacaaagtagggcaggcatgttgacagcccatcgccctttgatgatgacctg  
 L V S D K V G Q A C C R P I A F D D D L  
 tcgttttttagatgataacctgggtttaccatattctaagaaagcattccgctaaaagggtgt  
 S F L D D N L V Y H I L R K H S A K R C  
 ggatgtatctgatctaga  
 G C I -

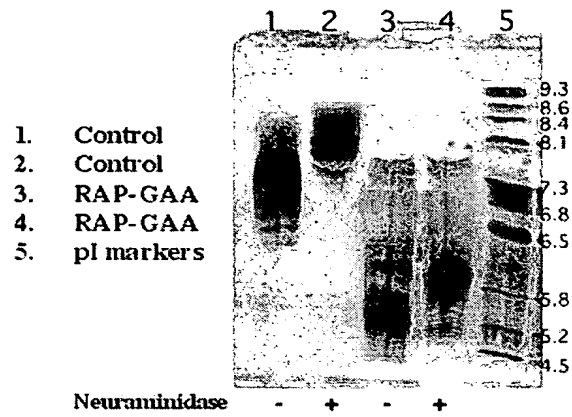
Linker peptide is underlined.

**Figure 6**



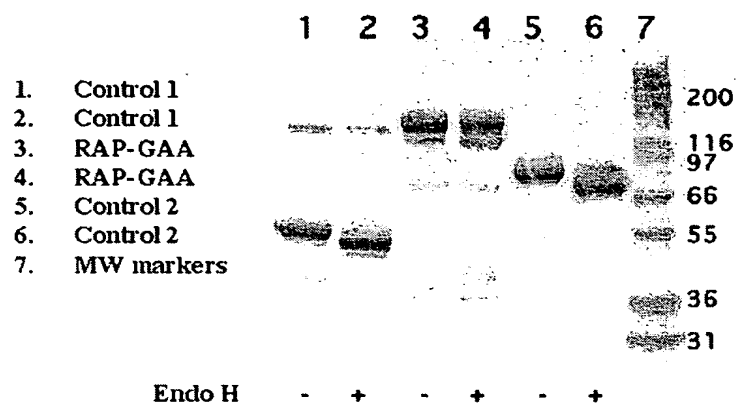
**Figure 7**

**Digestion of RAP-GAA with Neuraminidase**

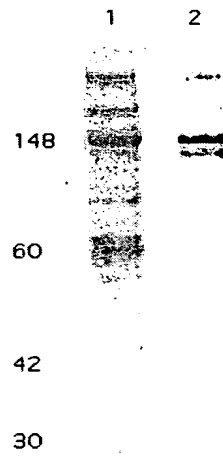


**Figure 8**

**Digestion of RAP-GAA with Endo H**








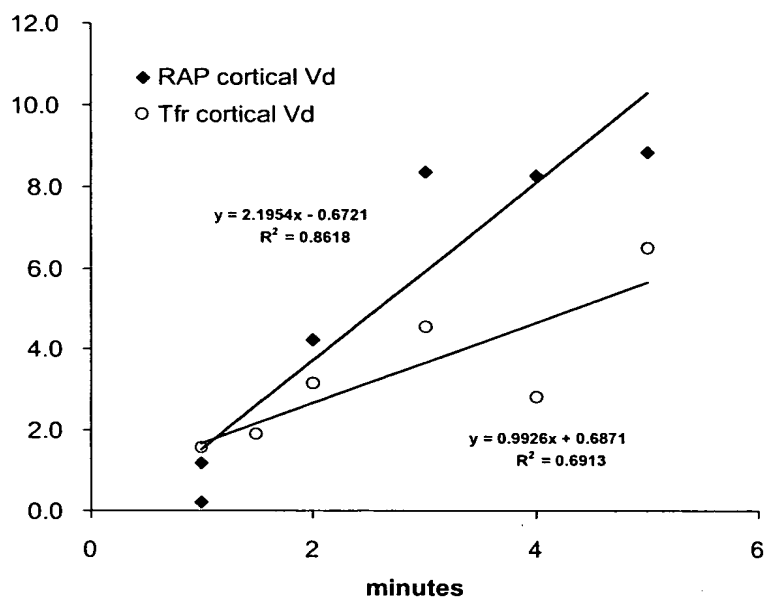
**Figure 9**



1. SDS-PAGE
2. Anti-Iduronidase Western

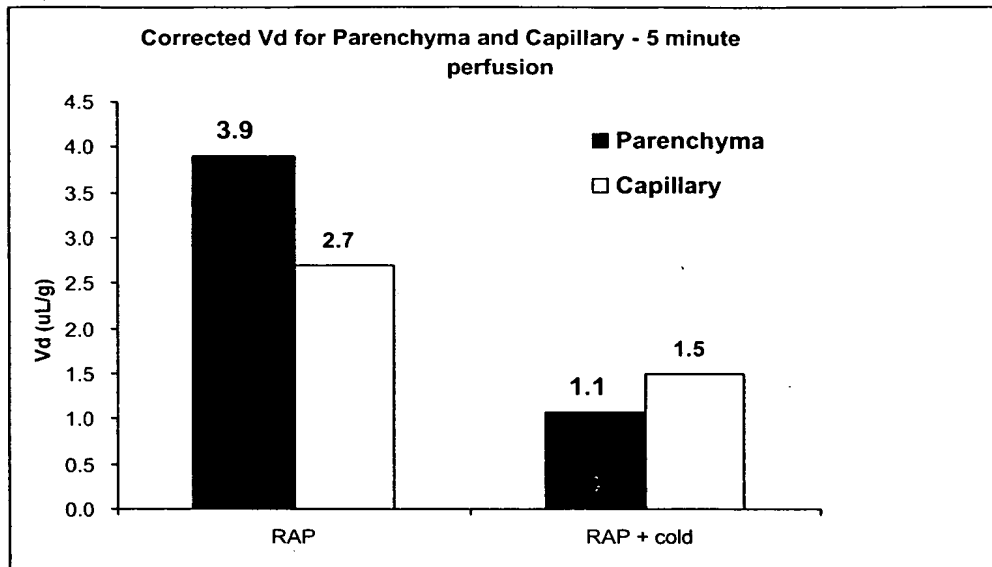
**Figure 10**

	None	RAP	RAP-Idu (Purified)	RAP-Idu (Medium)
Anti-RAP				
Anti-Idu				



Corrected  $V_d$  vs. Perfusion time.

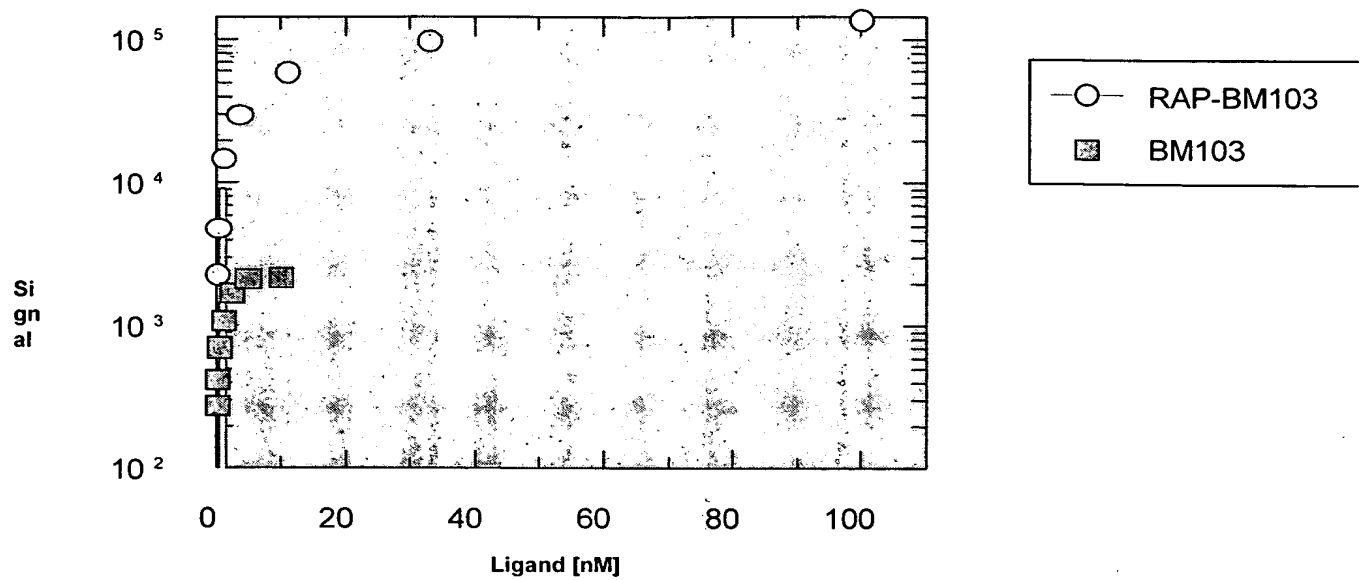
**Figure 11**



**Figure 12**



**RAP-BM103 Uptake by Human Fibroblast**  
BM103 cells (GM244)

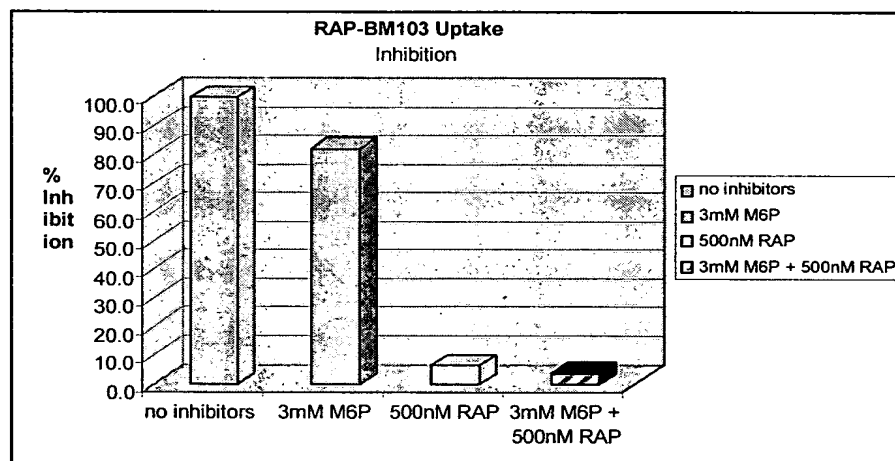


**RAP-BM103**

Parameter	Value	Std. Error
Vmax	160806 .4864	5540 .7619
Km	18 .6316	1 .8955

**BM103**

Parameter	Value	Std. Error
Vmax	2691 .6376	112 .1342
Km	1 .6615	0 .2002



**FIGURE 13**

FIGURE 14. Multiple alignment of amino acid sequences of RAP from different species.

human	1	-----MAPRRVRSFLRGLPALLLLLLFPGWPAASHGKGYSREK
mouse	1	MGGPTRSPVSLALQRKMAPRRERVSFLPRLQLLVLLLPMLVPQPIAGHGKGYSREK
rat	1	-----LRDRVSFLPRLQLLVLLLPMLVPQPIAGHGKGYSREK
chicken	1	-----MGATRTLVAVMAAFLAVSTRASKYAREA
zebrafish	1	-----MAGKYSKEM
fruit fly	1	-----MVRSAVVAAIALSVLIAIAGVDADKKQSKYSKEA
mosquito	1	-----ELCPIARRKRGIKHILTMPLFTRLCIVFTLVLCNVHVQSEKAHSKY
flatworm	1	-----MRNHSFLL
consensus	1	t 1 11 lml hggkysre

human	40	-----NPKPSPKRESGEFRMEKLNQWEKAQRLHLPVRLAELHDLKIQERDE
mouse	61	-----NEPEMAAKRESGEFRMEKLNQWEKAQRLHLPVRLAELHSDLKIQERDE
rat	40	-----NEPEMAAKRESGEFRMEKLNQWEKAQRLHLPVRLAELHSDLKIQERDE
chicken	29	-----NEGLADAKRREAGEFRVFLNQVWEKAQRLQSAVRLAELHSDLKIQEKDE
zebrafish	10	-----NEKNASDKSNNQVEFRILAKLNQVWEKAIRMLAPVRLSELHSDLKIQEKDE
fruit fly	37	NDPHFQQVKLEKYDPDFRSIQRPFRMAKLNLVWAKAQNRLTEPKLKSLYMELKHKEE
mosquito	48	SKHANALPDSEIIEYDPFRNIQRPFRMAKLNLVWTKAQRRLTEPKLKSLYTELKHKEE
flatworm	10	-----FLLVIGSAHNKKTQYRTERINFVEKALQHVTDRONLARLEKELSGYDAIY
consensus	61	ne kr g efrmeklnqvweKAqrl lspvrLaeLhsdLkigekde

human	91	LAWKKLKLGLDEDEGEKEAKLIRNLNVILAKYGLDGKKDARQVTSN-----SISGTOE--
mouse	112	LNWKKLKVEGLDKDGEKEAKLIRNLNVILAKYGLDGKKDAQMVHSN-----AINEDTQ--
rat	91	LNWKKLKVEGLDKDGEKEAKLIRNLNVILAKYGLDGKKDTQTQVHSN-----AINEDTQ--
chicken	80	LSWKKLKAEGLDGEDEGEKEAKLRNRNINVIITKYGMNGKDSHLTDIN-----YIKGTS-
zebrafish	61	LQWKKLKAEGLDGEDEGEKEAKLRNRNINILAKYGMNGKDKTRTIDSNR---LKDHEVKIG-
fruit fly	96	LAWKOLNSQHKDKDGLKADELRRKLIGIMSSYDLLEHFDTDQTEKLKPKKFKAEER-
mosquito	107	LTQKOLK--EKDKDGLKEAELRNKLVSIMSTYGLLEHFDTDQPEKYKLAKSSDGAPKKD
flatworm	61	LASKSNR--QGTQGTKEIDKIDDKLGKILEKYGLEKAVLAFKEKYKHKNLFQQTIDNEP-
consensus	121	1 wKklk egld dgekeaklrrnlvIlakYgldgkdd v sn 1 e e

human	144	-----DGLDDPRLEKLWHKAKTSGKFSGEELDKLWREFLHHKEKVIHEYNVLLLETLS----
mouse	165	-----DELGDPRLEKLWHKAKTSGKFSSEELDKLWREFLHYKEKIQEYNVLLLETLS----
rat	144	-----DELGDPRLEKLWHKAKTSGKFSSEELDKLWREFLHYKEKIQEYNVLLLETLS----
chicken	134	-----DTLDDPRLEKLWSKAKTSGKFSDEELDKLWREFKHHKEKIREYNVLLLETLS----
zebrafish	117	-----DTFDDPKLEKLWNKAKTSGKFSDEELQTLHREFQHHKQKIHEYNVVLETYS----
fruit fly	155	-HRNKSLFKDKKLNKLWEKAEISG-FTAEELKSLKQEFDDHHQDKVDVYYSLLLENIG----
mosquito	165	TYKNKSLFKDKKLNKLWDKAEISG-FTKEELDALREEFDHHQAKIDVYYSLLERLGDGDD
flatworm	118	--LPSGKFTDONLQKLWSQAQNGK-FSQKELNALHGELKEVECKERVYEDQLDDFK----
consensus	181	d DprLekLW kAktsgkFs eELdkLwrEf hhkeKiheYnvllletls

human	195	-----RTEEIHENNVISPSDLS-----DIKGSVLHSHHTELKDEL
mouse	216	-----RAEEGYENLISPSDMA-----HIKSDTLISKHSELKDEL
rat	195	-----RAEEGYENLISPSDMT-----HIKSDTLASKHSELKDEL
chicken	185	-----RTEEIHKKVINPSEEN-----PVKEEVLHNKHRELKDEL
zebrafish	168	-----RTEEIHKNMISPLEG-----DVKENVLHQKHTELKORM
fruit fly	209	-----TVDTLKHENAINTEDELDTYNLISNDVNENDIKTHAQNVSFENDLNTLGGH
mosquito	224	GGAAGQGSRRDDALLNAVNDDEHDYNEVDRAEETDRSQPGANKQOHAYLHKSNGLEKH
flatworm	171	-----K--VPHENSTOHDIIES-----IG--DKTKKLKAAN
consensus	241	r ee henvispsdl ik 1 khteLkek1

Figure 14A

human	229	RSINQGLDRLRRVSHQGYSTAEFEFEEPRVIDLWDLAQSA-NLTEKELESFREELKHFEAK
mouse	250	RSINQGLDRLRRVSHQGYGSTAEFEFEEPRVIDLWDLAQSA-NFTEKELESFREELKHFEAK
rat	229	RSINQGLDRLRRVSHQGYGPAEFEEPRVIDLWDLAQSA-NFTEKELESFREELKHFEAK
chicken	219	RSINQGFERLRVSHQGYDATSEFEFEEPRVIDLWDMAKSA-NFTEKELESFREELKHFEAK
zebrafish	201	RDINQGFERLRKTHHEGYTDDSEFREPRVIELWEMAKRS-NLSEDELESLEELNHFETK
fruit fly	261	TGIKDHDRLELVSSGPHSQ-DFTEPKVQGLWRVAQAS-NFTVKELESITELNHFESR
mosquito	284	REIRDNFDRLDPASKGPKSQ-DFVEPKVQGLWRVALAS-LFSADELASLVELLNHFESR
flatworm	197	REINDHLDEVHRKVTSEEFSP--FNEPRVKRLWKLAQENEKLTPELSVLDDELNHFESQ
consensus	301	rsinqgldrlrrvshqgy s teFeEPrVidLWdlAqsa nftkeLEsfreELkHfEak
human	288	IEKHHHYQKQLEISHKLEKHAE-----VGDERVSRSEKHALLEGTKELGYTVKKHL
mouse	309	IEKHHHYQKQLEISHOKLKHVES-----GDPEHISRNEKYVLLEEKTKELGYKVKKHL
rat	288	IEKHHHYQKQLEISHOKLKHVES-----GDPEHISRNEKYVLLEEKTKELGYKVKKHL
chicken	278	IEKHHHYQKQLEISHEKLEKHTEG-----TGDKEHLNRNREKYANLEEKTKELGYKVKKHL
zebrafish	260	VEKHHHYQEQLEISHOKLKHVEA-----LGDEDHIMRNREKYNTLAEKARENGYKVKKKHL
fruit fly	319	LLKLRHLHAHHAHQEKYKGEK-----VKDKSSRFEEMEDQLKKQTRKVEKLO
mosquito	342	LLKLRHMHAEHAHSLKHKHS-----DAKADTHKLMEENIKKQTRKVEKMO
flatworm	255	LKKIEFHKVFFVANSCKPKRGKNEEVSRLOEDAEERGKDKSQVYENLELSIKHEKLNKKA
consensus	361	ieKhnhyqkqleisheklkhve vgd ehv rnrëky lleektkelgykvkkhl
human	343	QDLSSGRISF--ARHNEL
mouse	364	QDLSSRVSR--ARHNEL
rat	343	QDLSSRVSR--ARHNEL
chicken	333	QDLSSRISQG-LQHNEL
zebrafish	315	QDLINKEISANGLOHNEL
fruit fly	367	ENIEKTIFK----HTEL
mosquito	388	EEVERRIFK----HSEL
flatworm	315	RKLEKYIEEKIIHREL
consensus	421	qdls risr HnEL

Figure 14B

**Figure 15: SEQ ID NO: 1:**

TyrSerArgGluLysAsnGlnProLysProSerProLysArgGluSer  
GlyGluGluPheArgMetGluLysLeuAsnGlnLeuTrpGluLysAla  
GlnArgLeuHisLeuProProValArgLeuAlaGluLeuHisAlaAsp  
LeuLysIleGlnGluArgAspGluLeuAlaTrpLysLysLeuLysLeu  
AspGlyLeuAspGluAspGlyGluLysGluAlaArgLeuIleArgAsn  
LeuAsnValIleLeuAlaLysTyrGlyLeuAspGlyLysLysAspAla  
ArgGlnValThrSerAsnSerLeuSerGlyThrGlnGluAspGlyLeu  
AspAspProArgLeuGluLysLeuTrpHisLysAlaLysThrSerGly  
LysPheSerGlyGluGluLeuAspLysLeuTrpArgGluPheLeuHis  
HisLysGluLysValHisGluTyrAsnValLeuLeuGluThrLeuSer  
ArgThrGluGluIleHisGluAsnValIleSerProSerAspLeuSer  
AspIleLysGlySerValLeuHisSerArgHisThrGluLeuLysGlu  
LysLeuArgSerIleAsnGlnGlyLeuAspArgLeuArgArgValSer  
HisGlnGlyTyrSerThrGluAlaGluPheGluGluProArgValIle  
AspLeuTrpAspLeuAlaGlnSerAlaAsnLeuThrAspLysGluLeu  
GluAlaPheArgGluGluLeuLysHisPheGluAlaLysIleGluLys  
HisAsnHisTyrGlnLysGlnLeuGluIleAlaHisGluLysLeuArg  
HisAlaGluSerValGlyAspGlyGluArgValSerArgSerArgGlu  
LysHisAlaLeuLeuGluGlyArgThrLysGluLeuGlyTyrThrVal  
LysLysHisLeuGlnAspLeuSerGlyArgIleSerArgAlaArgHis  
AsnGluLeu

**Figure 16: SEQ ID NO: 2:**

ProArgLeuGluLysLeuTrpHisLysAlaLysThrSerGlyLysPhe  
SerGlyGluGluLeuAspLysLeuTrpArgGluPheLeu HisHisLys  
GluLysValHisGluTyrAsnValLeuLeuGluThrLeuSerArgThr  
GluGluIleHisGluAsnValIleSerProSerAspLeuSerAspIle  
LysGlySerValLeuHisSerArgHisThrGluLeuLysGluLysLeu  
ArgSerIleAsnGlnGlyLeuAspArgLeuArgArgValSerHisGln  
GlyTyrSerThrGluAlaGluPheGluGluProArgValIleAspLeu  
TrpAspLeuAlaGlnSerAlaAsnLeuThrAspLysGluLeuGluAla  
PheArgGluGluLeuLysHisPheGluAlaLysIleGluLysHisAsn  
HisTyrGlnLysGlnLeuGluIleAlaHisGluLysLeuArgHisAla  
GluSerValGlyAspGlyGluArgValSerArgSerArgGluLysHis  
AlaLeuLeuGluGlyArgThrLysGluLeuGlyTyrThrValLysLys  
HisLeuGlnAspLeuSerGlyArgIleSerArgAlaArgHisAsnGlu  
Leu

Figure 17

## Transport assays in BBCEC monolayers

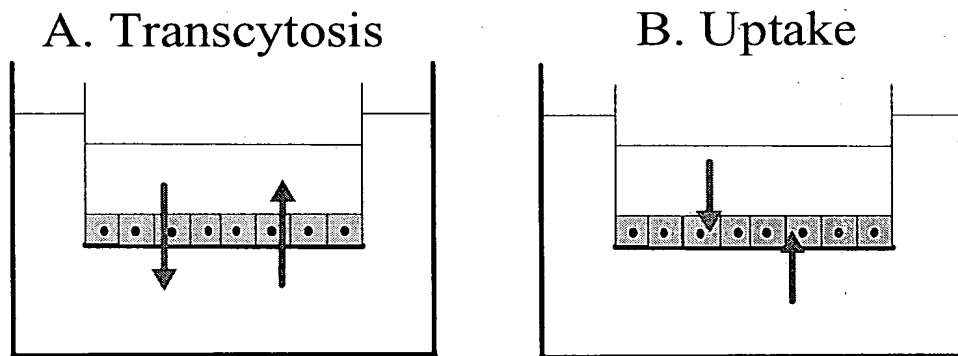


Figure 18

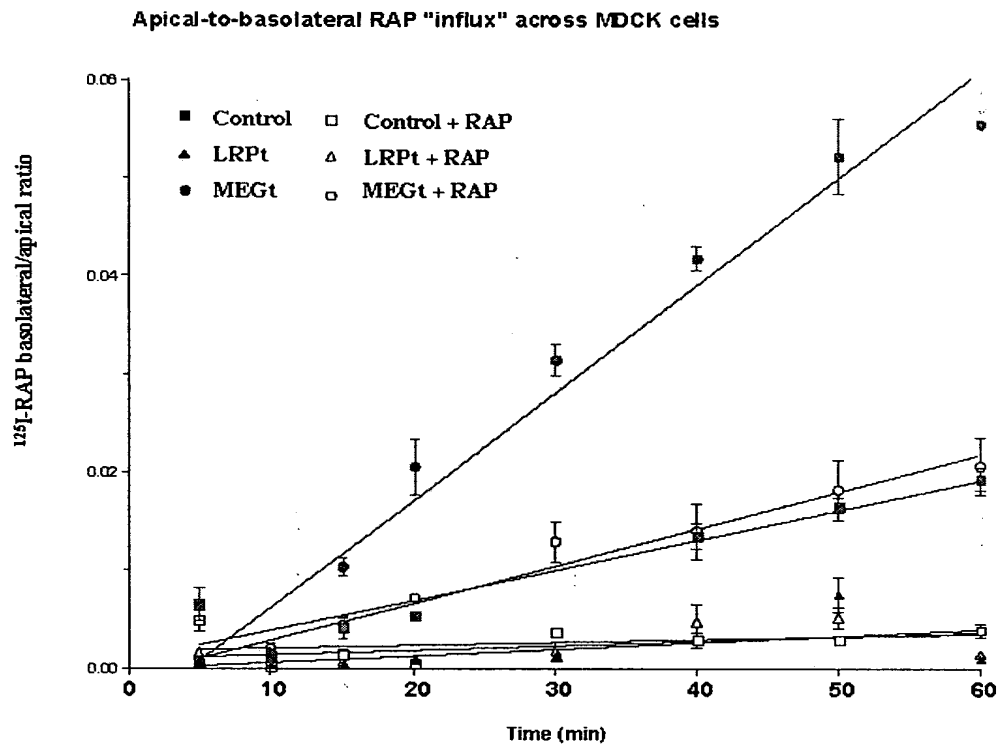


Figure 19A

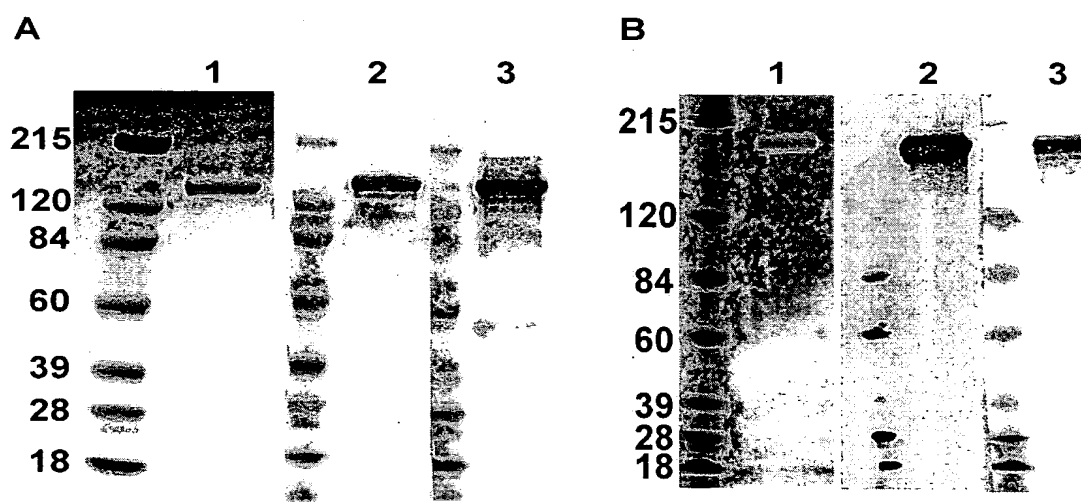
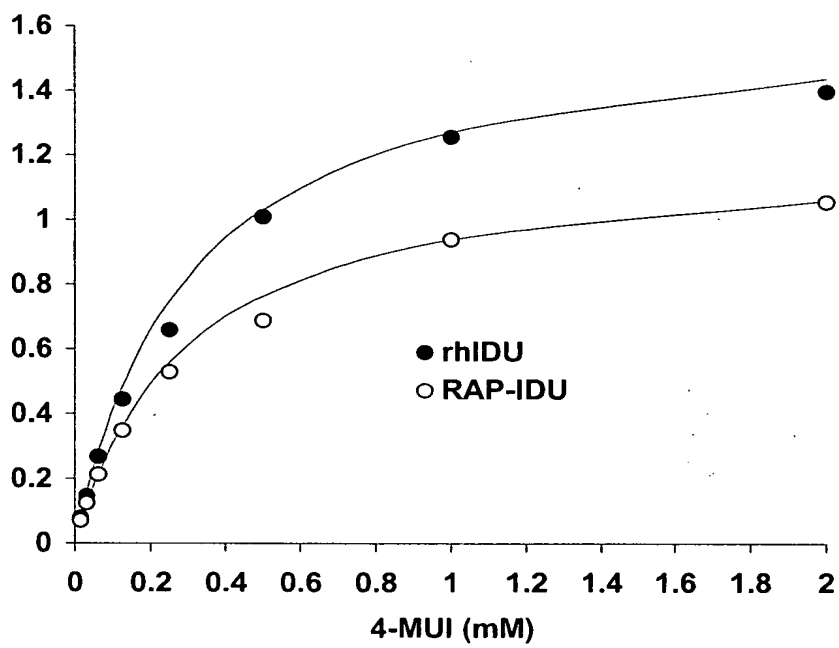




Figure 19B



**Figure 19C**

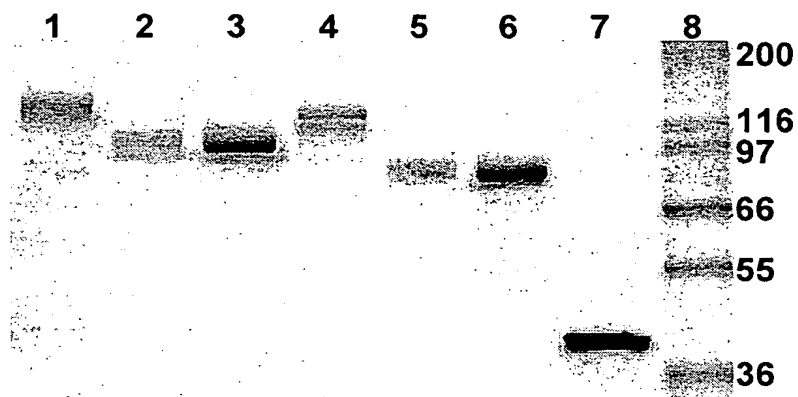


Figure 20A

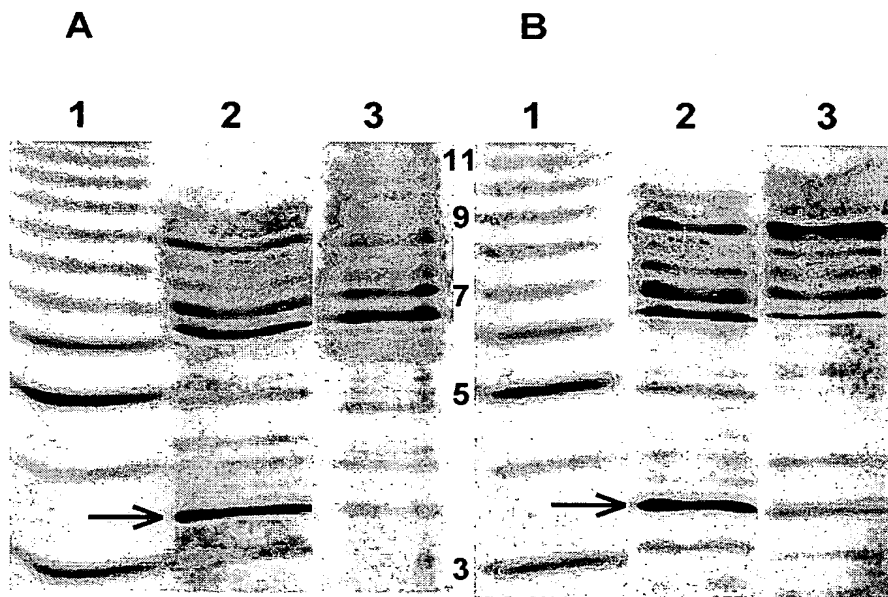
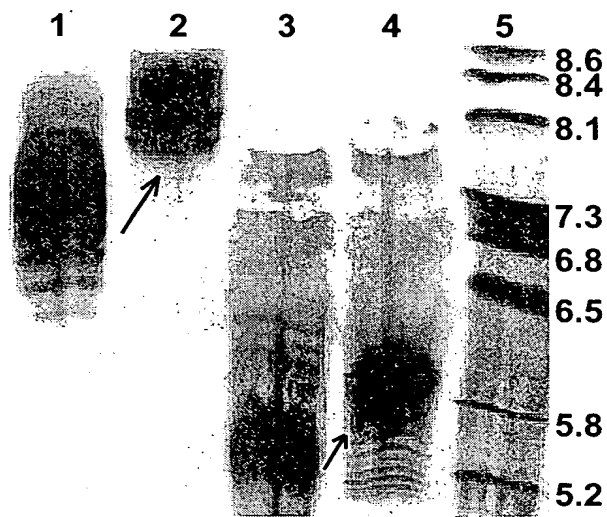
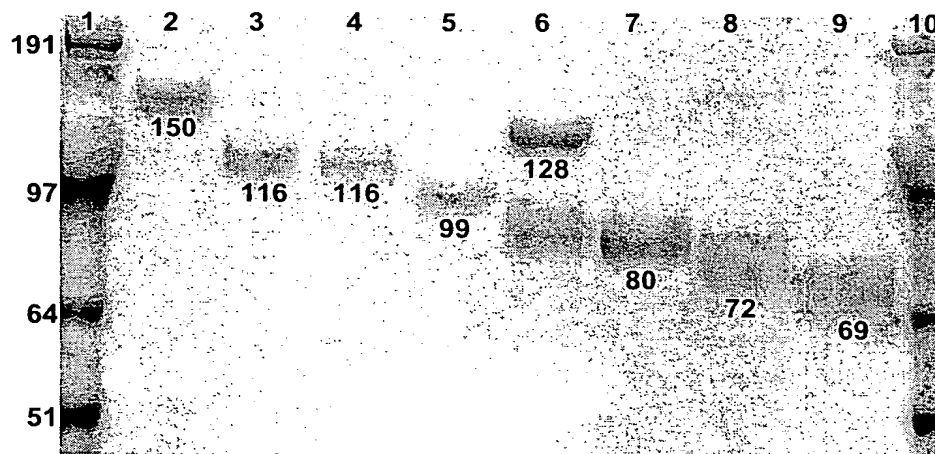


Figure 20B





**Figure 21**

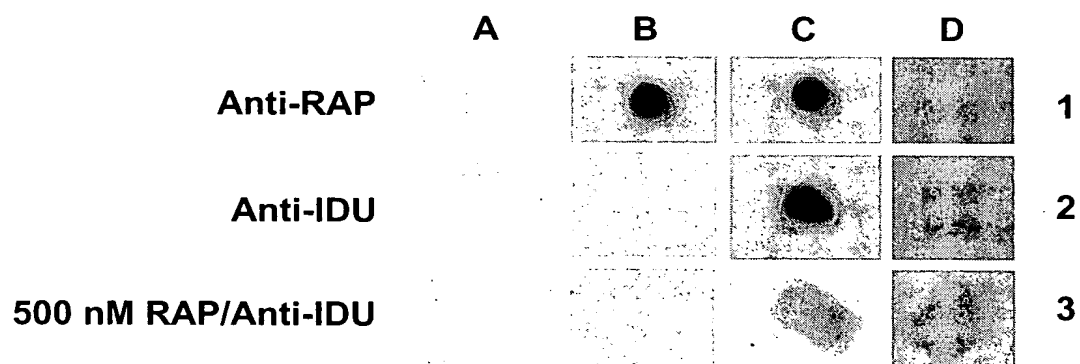


Figure 22A

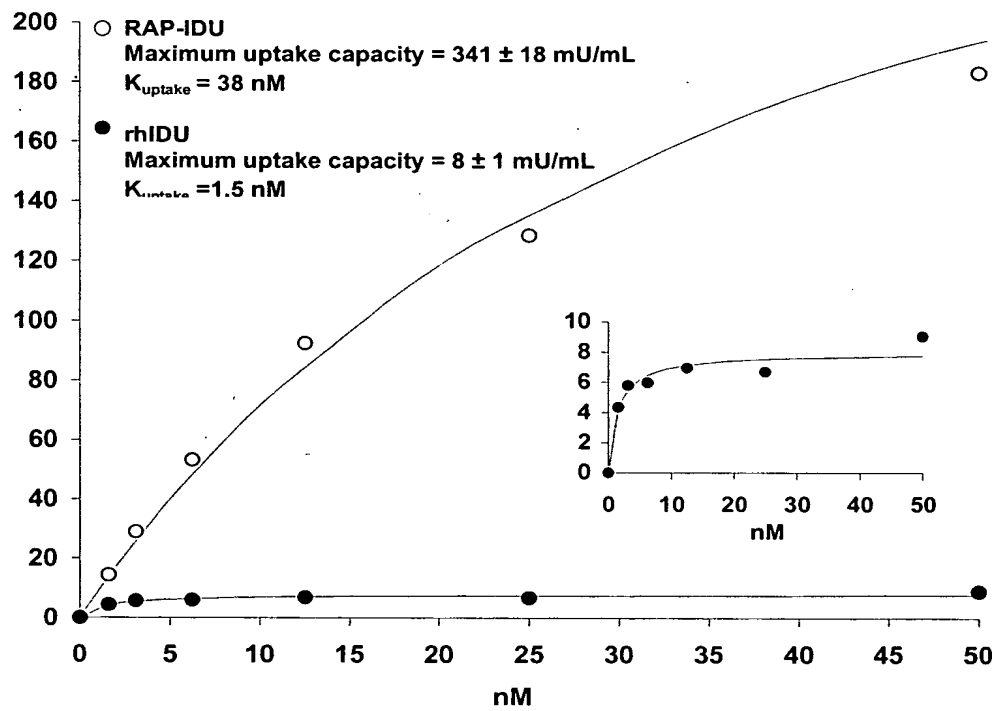


Figure 22B

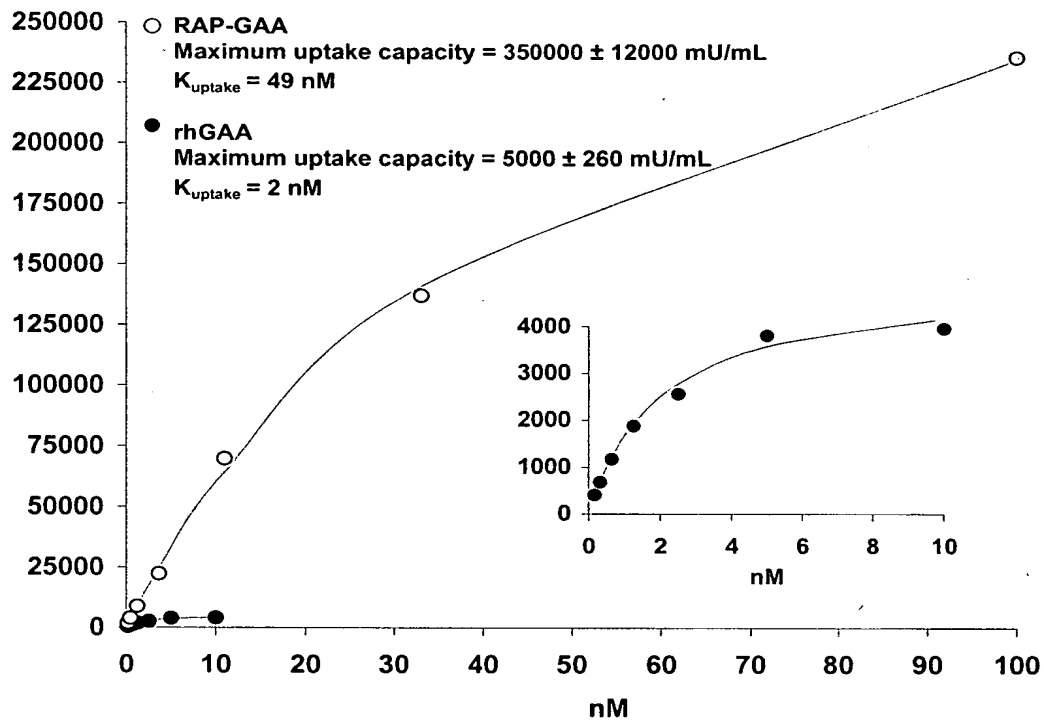




Figure 22C

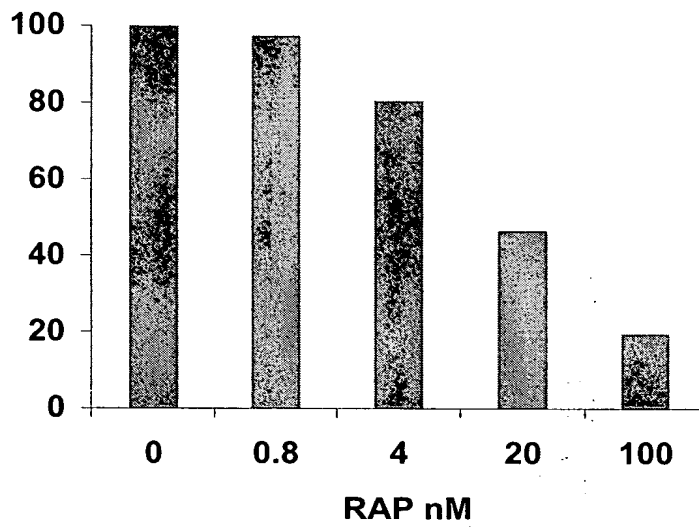


Figure 22D

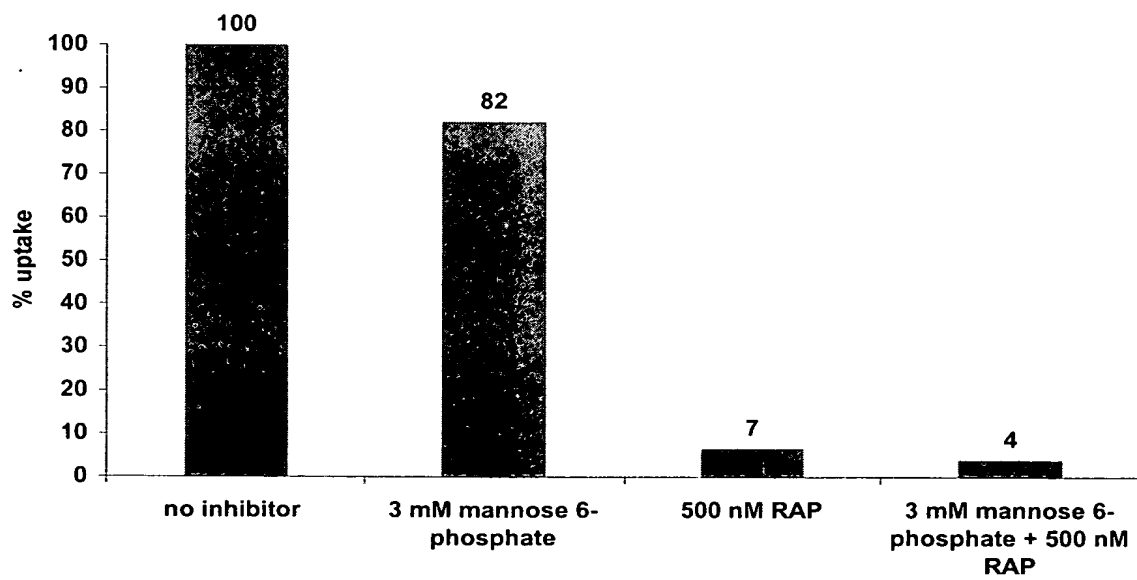
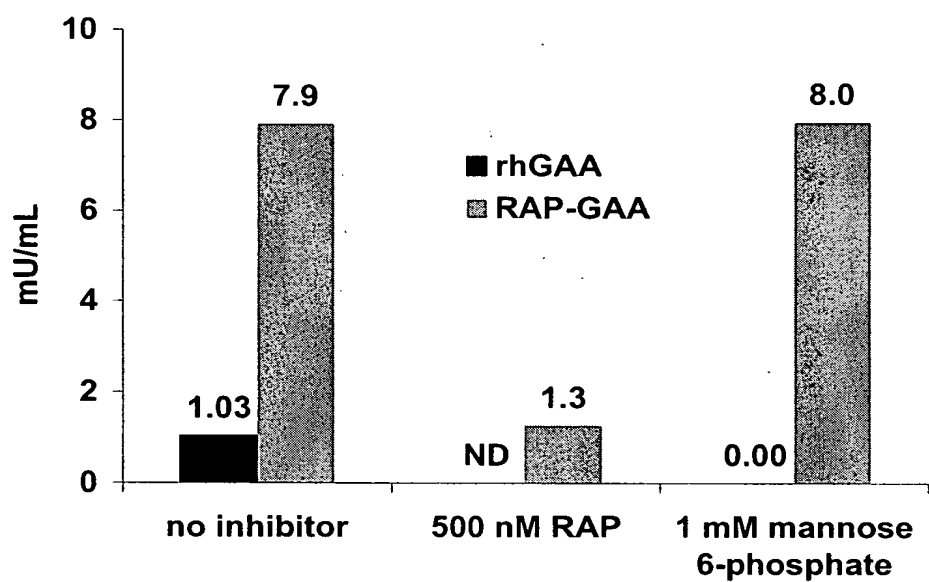
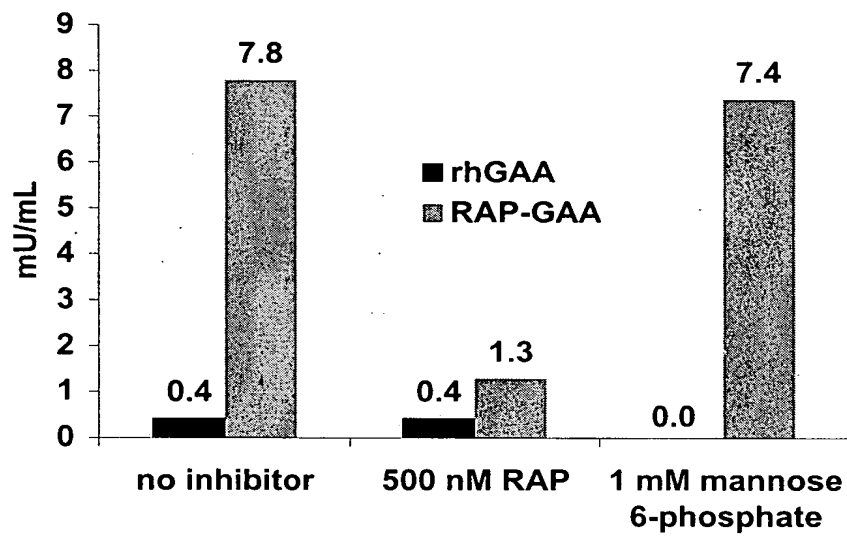


Figure 22E



**Figure 22F**



**Figure 23**

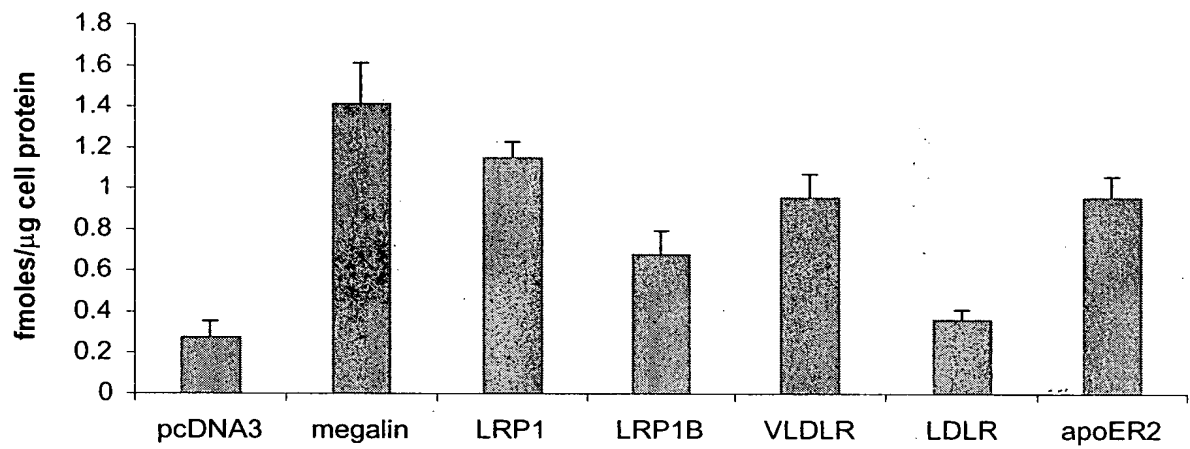


Figure 24

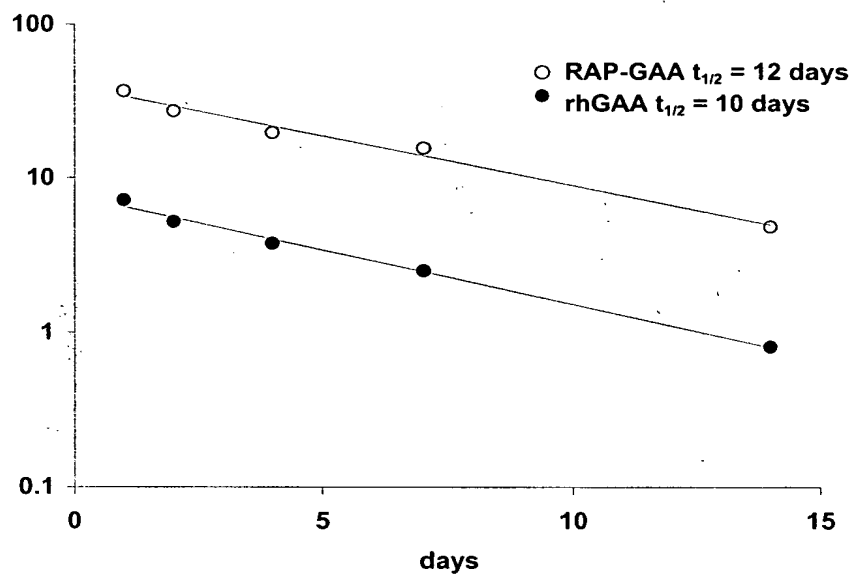


Figure 25A and Figure 25B

